

REMARKS

Status Of Claims

New claims 120 to 129 have been added. Those claims are supported by the specification, e.g., at pages 39 to 42 and Figure 4.

Claims 52 to 86 and 115 to 129 are presently under consideration.

Rejection In View of Barany PCT

The Examiner rejected claims 52 to 64, 69 to 80, 85, 86, and 115 to 117 under 35 U.S.C. § 102(b) as allegedly being anticipated by WO 97/31256 (Barany PCT). See Action at page 2. The Examiner cites various text of Barany PCT as allegedly showing various aspects of certain claims. See *id.* at pages 3 to 4. Applicant respectfully traverses that rejection.

Independent claim 115 recites a probe that comprises “an addressable support-specific portion located between the primer-specific portion and the target-specific portion.” Independent claims 52 and 60 recite that “at least one probe in each probe set further comprises an addressable support-specific portion located between the primer-specific portion and the target-specific portion.” Independent claim 71 recites that “at least one second probe in each probe set further comprises an addressable support-specific portion located between the primer-specific portion and the target-specific portion.”

The Examiner first contends that Barany PCT discusses a probe set that includes two probes that are suitable for ligation together and that each includes a target specific portion and an addressable array portion. See *id.* at pages 2 to 3. The Examiner

further contends that the terminal nucleotides of the addressable array portions of each probe can inherently function as a primer-specific portion. See *id.* at pages 4 to 5.

The Examiner then contends that, "with regard to the orientation of the primer region and the addressable region, it is noted that in an oligonucleotide, these terms represent intended use limitations and do not structurally effect the oligonucleotide." See *id.* at page 4. The Examiner then illustrates his position by showing that an exemplary nucleotide split into two or three separate portions is the same nucleotide irrespective of the intended properties of each portion. See *id.* The Examiner further states that "any region of any oligonucleotide is inherently and necessarily capable of function as a primer target region, or as an addressable region or as a target specific region, which specificity is solely dependent upon experimental selection of the appropriate primer, capture probe or target." See *id.* at pages 4 to 5.

Applicants respectfully assert that the Examiner has not established that Barany PCT anticipates any of the present claims. As discussed above, all of applicants independent claims recite a probe that comprises an addressable support-specific portion located between the primer-specific portion and the target-specific portion. Thus, each of those claims includes a probe that comprises three specific portions that have three different functions, and those three specific portions are arranged in a particular order. Moreover, the three specific functions require the three specific portions to have particular structure. Thus, the three specific portions do affect the structure of the probe.

The Examiner does not contend that Barany PCT actually shows or even suggests a probe that has the three specific portions with the three different functions

according to the present claims. Rather, the Examiner contends that Barany PCT shows a probe with two specific portions with two different functions. Specifically, the Examiner contends that Barany shows a probe with an allele specific portion and an addressable sequence on the 5' end that hybridizes to a complementary sequence on an addressable array. See Barany PCT at page 12, lines 25 to 29. The Examiner then contends that Barany PCT need not actually show or even suggest the third specific portion, a primer-specific portion, as set forth in the present claims. The Examiner reaches that conclusion by contending that primers can be designed for all oligonucleotides, and thus, the addressable sequence on the 5' end of the Barany PCT probe is also capable of being a primer-specific portion.

First, to establish anticipation, the Examiner must establish that the art shows every limitation of the claims. The fact that someone could design primers that hybridize with the addressable sequence in Barany PCT does not convert Barany PCT into a teaching of a probe comprising the three specific portions with the three different functions. The Examiner presents no reason why one skilled in the art would design a primer specific for the addressable sequence in the Barany PCT probe. In fact, Barany discusses hybridizing the ligation product, which includes the addressable sequence, directly to an array without amplification of the ligation product. The Examiner provides no reason why one skilled in the art would design the addressable sequence of the Barany PCT probe to also serve as a primer-specific portion, since there is no suggested amplification of the ligation product in Barany PCT. Accordingly, Barany fails to teach, inherently or otherwise, a probe comprising the three specifically claimed portions with the three specific functions.

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Second, the fact that someone could design the same oligonucleotide sequence to include two or three specific portions with different functions in different orientations does not convert Barany PCT into a teaching of a probe comprising the three specific portions with the three specific functions in the specific order as presently claimed. As discussed above, the Examiner provides no reasons why one skilled in the art would design the Barany PCT probes to include a primer-specific portion. Absent such reasons, it is further unclear why the Examiner contends that one skilled in the art would design the Barany PCT probe to include an addressable support-specific portion between a primer-specific portion and a target-specific portion.

For at least these reasons, the Examiner has failed to establish that Barany PCT would have shown or suggested claims 52, 60, 71, and 115, and all claims dependent from those claims. Thus, applicants need not address the Examiner's contentions concerning the other limitations of those claims. By not addressing those contentions, applicants in no way acquiesce to those contentions.

Also, dependent claims 53, 62, and 73 recite kits that further comprise one or more primers in addition to at least one probe set. The Examiner failed even to assert that Barany PCT showed primers in addition to probes. Accordingly, the Examiner failed to establish that Barany PCT shows or suggests claims 53, 62, and 73 for at least this additional reason.

Applicant respectfully requests reconsideration and withdrawal of the § 102 rejection of certain claims in view of Barany PCT.

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Rejection In View of Barany US

The Examiner rejected claims 52 to 63, 69 to 79, 85, 86, and 115 to 117 under 35 U.S.C. § 102(a) and (e) as allegedly being anticipated by US Patent No. 6,027,889 (Barany US). See Action at page 5. The Examiner cites various text of Barany US as allegedly showing various aspects of certain claims. See *id.* at pages 5 to 6. Applicant respectfully traverses that rejection.

Independent claim 115 recites a probe that comprises “an addressable support-specific portion located between the primer-specific portion and the target-specific portion.” Independent claims 52 and 60 recite that “at least one probe in each probe set further comprises an addressable support-specific portion located between the primer-specific portion and the target-specific portion.” Independent claim 71 recites that “at least one second probe in each probe set further comprises an addressable support-specific portion located between the primer-specific portion and the target-specific portion.”

The Examiner first contends that Barany US discusses a probe set that includes two probes that are suitable for ligation together and that each includes a target specific portion, an addressable array portion, and a region which functions as a primer-specific portion. See *id.* at page 5.

The Examiner then contends that, “with regard to the orientation of the primer region and the addressable region, it is noted that in an oligonucleotide, these terms represent intended use limitations and do not structurally effect the oligonucleotide.” See *id.* at page 6. The Examiner then illustrates his position by showing that an exemplary nucleotide split into two or three separate portions is the same nucleotide

irrespective of the intended properties of each portion. See *id.* at pages 6 to 7. The Examiner further states that "any region of any oligonucleotide is inherently and necessarily capable of function as a primer target region, or as an addressable region or as a target specific region, which specificity is solely dependent upon experimental selection of the appropriate primer, capture probe or target." See *id.* at page 7.

Applicants respectfully assert that the Examiner has not established that Barany US anticipates any of the present claims.

First, independent kit claims 52, 60, and 71 require at least one probe set comprising at least one first probe and at least one second probe that are suitable for ligation together, wherein at least one probe in a probe set comprises an addressable support-specific portion located between the primer-specific portion and the target-specific portion.

Contrary to the allegations of the Examiner, Barany US failed to disclose or suggest such a probe set. In fact, Barany fails to disclose a probe set that comprises at least one first probe and at least one second probe that are suitable for ligation together, wherein at least one probe in the probe set comprises an addressable support-specific portion located between the primer-specific portion and the target-specific portion. Rather, Barany discusses the use of a primer in the PCR reaction (not a probe that is suitable for ligation to another probe in the probe set), that contains an addressable array-specific portion linked to the 5' end of the primer. See Barany at column 28, lines 23 to 56. The Examiner fails to explain why a discussion of a PCR primer that contains an addressable array-specific portion linked to the 5' end of the

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primer would have shown or suggested a probe set according to any of independent claims 52, 60, and 71.

For at least this reason, the Examiner has failed to establish that Barany would have shown or suggested claims 52, 60, and 71, and all claims dependent from those claims. Thus, applicants need not address the Examiner's contentions concerning the other limitations of those claims. By not addressing those contentions, applicants in no way acquiesce to those contentions.

Second, as discussed above, all of applicants independent claims recite a probe that comprises an addressable support-specific portion located between the primer-specific portion and the target-specific portion. Thus, each of those claims includes a probe that comprises three specific portions that have three different functions, and those three specific portions are arranged in a particular order. Also as discussed above, the three specific portions affect the structure of the probe.

As discussed above, to establish anticipation, the Examiner must establish that the art shows every limitation of the claims. The fact that someone could design the same oligonucleotide sequence to include two or three specific portions with different functions in different orientations does not convert Barany US into a teaching of a probe comprising the three specific portions with the three specific functions in the specific order as presently claimed. In fact, in view of the actual teachings of Barany US, the Examiner has failed to establish that Barany US would have taught designing a probe with an addressable support-specific portion located between a primer-specific portion and a target-specific portion.

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Specifically, Barany US discusses using two probes that, when the correct target is present, are ligated together to form a ligation product.¹ The ligation product is then amplified with PCR primers. In certain embodiments, one of the PCR primers includes an addressable array-specific portion linked to the 5' end, and the addressable array-specific portion remains single stranded after the PCR reaction. The other primer includes a label. Barany US notes that the addressable array-support specific portion may remain single stranded by using a primer that includes the addressable array-specific portion and includes a non-natural base that prevents polymerase extension between the primer and the addressable array-specific portion. Thus, the strand created with such a primer will not be extended past the primer into the addressable array-specific portion when the other primer is being extended. Different capture oligonucleotides are disposed on an array to hybridize to the addressable array-specific portion of the amplification products to capture the amplification products. The label on the strand opposite the strand containing the addressable array-specific portion is then detected.

The Examiner contends that the orientation of the primer-specific portion and the addressable array-specific portion are not important with respect to oligonucleotides because the intended use of such portions does not structurally affect the oligonucleotide. Therefore, the Examiner apparently is asserting that one skilled in the art would consider that the specific primer in Barany US inherently could have the 5' upstream primer-specific portion at the 5' end of the primer and the addressable array-specific portion spaced from that end. The Examiner, however, fails to explain how

¹ The discussion of Barany in this paragraph is from Barany at column 26, line 37, to column 27, line 19.

such a rearranged structure of the Barany US primer would work in the Barany US process.

If one were to attempt to use such a redesigned primer for amplifying the ligation product in Barany US, the ligation product in Barany US would have to already include an addressable array-specific portion. The Examiner provides no explanation of how the applied art would have suggested that the prior hybridization and ligation reaction of Barany US should employ a probe that includes an addressable array-specific portion. Rather, the addressable array-specific portion in Barany US is added by the primer in a subsequent amplification step.

Second, the amplification product that is immobilized on the array in Barany US includes a double stranded portion that includes one strand with the label and the other strand with the single stranded tail that includes the addressable array-specific portion. If the addressable array-specific portion were not on the 5' end of the primer in Barany US, the Examiner has not explained how one would obtain an amplification product that includes a single stranded addressable array-specific portion on one strand and a label on the other strand as taught by Barany US.

Thus, without explaining how one would use such a rearranged structure in the Barany US process, the Examiner failed to establish how Barany US would have taught one skilled in the art to make a probe comprising an addressable support-specific portion located between the primer-specific portion and the target-specific portion according to present independent claims 52, 60, 71, and 115.

For at least these reasons, the Examiner has failed to establish that Barany US would have shown or suggested claims 52, 60, 71, and 115, and all claims dependent

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from those claims. Thus, applicants need not address the Examiner's contentions concerning the other limitations of those claims. By not addressing those contentions, applicants in no way acquiesce to those contentions.

Applicant respectfully requests reconsideration and withdrawal of the § 102 rejection of certain claims in view of Barany US.

Rejection In View of Barany PCT and Xu

The Examiner also rejected several claims under 35 U.S.C. § 103(a) as allegedly being unpatentable over Barany PCT in view of Xu et al., *Tetrahedron Lett.*, 38(32):5595-5598 (1997) (Xu). See Action at page 7. The Examiner cited Barany PCT for the reasons discussed in the prior rejections and stated that Barany PCT did not teach use of tosylated or iodate oligonucleotides for ligation. See *id.* (Certain dependent claims specifically recite that "the 5' thymidine leaving group is tosylate or iodide.") The Examiner contended that Xu discussed tosylated and iodate oligonucleotides for ligation. See *id.* Applicants respectfully traverse.

All of the dependent claims that specifically recite that "the 5' thymidine leaving group is tosylate or iodide" ultimately depend from one of independent claims 52, 60, 71, or 115. Thus, all of those dependent claims include all of limitations of the claims from which they ultimately depend. Above, applicants explained why the Examiner failed to establish that Barany PCT showed or would have suggested independent claims 52, 60, 71, and 115. Xu would have failed to remedy those deficiencies of Barany PCT.

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Thus, the Examiner has failed to establish that the combination of Barany PCT and Xu would have rendered obvious any of the rejected claims. Moreover, applicants need not address the Examiner's contentions concerning the combination of Barany PCT and Xu with respect to other limitations of certain dependent claims. By not addressing those contentions, applicants in no way acquiesce to those contentions.

Applicants respectfully request reconsideration and withdrawal of the § 103 rejections of certain claims in view of Barany PCT and Xu.

Rejection In View of Barany PCT and Boyce-Jacino

The Examiner rejected claims 52 to 64, 69 to 80, 85, 86, and 115 to 117 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Barany PCT in view of WO 99/66076 (Boyce-Jacino). See Action at page 8. The Examiner notes that he cites Boyce-Jacino as allegedly teaching a primer-specific portion to be used with the probe of Barany PCT if the anticipation rejection that relies upon the alleged inherency of such a primer-specific portion is reversed. See *id.*

The Examiner cites various text of Barany PCT as allegedly showing various aspects of certain claims. See *id.* at pages 8 to 9.

Independent claim 115 recites a probe that comprises "an addressable support-specific portion located between the primer-specific portion and the target-specific portion." Independent claims 52 and 60 recite that "at least one probe in each probe set further comprises an addressable support-specific portion located between the primer-specific portion and the target-specific portion." Independent claim 71 recites that "at least one second probe in each probe set further comprises an addressable support-

specific portion located between the primer-specific portion and the target-specific portion."

The Examiner first contends that Barany PCT discusses a probe set that includes two probes that are suitable for ligation together and that each includes a target specific portion and an addressable array portion. See *id.* at pages 8 to 9. The Examiner further contends that the terminal nucleotides of the addressable array portions of each probe can inherently function as a primer specific portion. See *id.* at page 9.

The Examiner further contends that Boyce-Jacino "teaches embodiments of probes which teaches that the addressable or capture region can be rearranged with the primer to form a primer, capture, target binding arrangement (see pages 13-18)." See *id.* at page 10. Specifically, the Examiner quotes Boyce-Jacino as follows: "In another preferred embodiment, the capture moiety comprises a specific sequence complementary to a PCR primer or portion thereof, used to amplify a region of the template strand." See *id.*

The Examiner concludes that it would have been obvious for one skilled in the art "to utilize the rearranged primer as taught by Boyce-Jacino in the method of Barany in order to permit amplification of the template strand within the primer in a nested PCR type reaction." See *id.* The Examiner further contends that an "ordinary practitioner would have been motivated to modify the Barany primer to include a primer sequence within the capture moiety in order to permit amplification of the template strand and to permit nested amplification." See *id.* Applicant respectfully traverses the rejection.

First, the Examiner has failed to provide sufficient evidence or rationale supporting the proposed combination of the alleged teachings of Barany PCT and

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Boyce-Jacino. As discussed above, Barany PCT fails to discuss amplification of the ligation products that include the ligated probe with an addressable sequence. Thus, the Examiner has not established why there would have been any motivation on the part of one skilled in the art to reach to Boyce-Jacino for a teaching about amplification primers for amplifying such ligation products. The Examiner simply fails to explain why one skilled in the art would have used the alleged “rearranged primer of Boyce-Jacino in the method of Barany . . .” when Barany PCT fails to discuss a method of amplifying the ligation product that includes an addressable sequence.

When the U.S. Patent and Trademark Office makes “core factual findings in a determination of patentability, . . .” the Office “must point to some concrete evidence in the record to support [such] findings.” *In re Zurko*, 59 U.S.P.Q.2d 1693, 1697 (Fed. Cir. 2001). Moreover, the Office “cannot rely on conclusory statements when dealing with particular combinations of prior art and specific claims, but must set forth the rationale on which it relies.” *In re Lee*, 61 U.S.P.Q.2d 1430, 1435 (Fed. Cir. 2002).²

Here, the Examiner provides neither concrete evidence on the record nor a suitable rationale why one of ordinary skill in the art would have been taught to use the alleged rearranged primer of Boyce-Jacino to amplify addressable sequences in the Barany PCT ligation product, when Barany PCT discusses no amplification of such ligation products. Moreover, the Examiner has not explained how Boyce-Jacino would have provided such motivation to modify the Barany PCT method. In fact, the Examiner provides no evidence of record or rationale for his statement that the ordinary practitioner would have been motivated to modify the Barany PCT primer to include a

2 Applicants enclose copies of the *Zurko* and *Lee* cases.

primer sequence within the capture moiety. The Examiner has pointed to no such motivation in either applied document. In fact, the Examiner points to no disclosure in Barany PCT of a primer, which is used for amplifying the addressable sequence, that could be modified.

Also, contrary to the contention of the Examiner, Boyce-Jacino fails to suggest a probe or primer that includes "a primer, capture, target binding arrangement." See Action at page 10. First, if the quoted section of Boyce-Jacino refers to the possibility of using a primer that includes a primer portion at the end and a capture region downstream from that end in the direction of extension, the capture region must already be included on the template being amplified. Otherwise, the template would not be extended past the portion that is complimentary to the primer portion of the primer. That primer includes no additional target binding region.

The other construct discussed by Boyce-Jacino, a "sequence reagent," also does not include a primer, capture, target binding arrangement. The sequence reagent includes a "capture moiety," a spacer, and a primer (see Figure 1 of Boyce-Jacino). Boyce-Jacino indicates that the capture moiety is used to capture target template in a sample to immobilize it to a spot on an array. See Boyce-Jacino, e.g., at page 26 and Figure 2. A spacer region is provided between the capture moiety and the primer of the sequence reagent to allow the primer to "scan" the immobilized target template for a complementary region on the target. See *id.* If a complementary region is found, primer extension is carried out to extend the sequence reagent on the end opposite to the capture moiety. See *id.* In fact, the sequence reagent of Boyce-Jacino is not subjected to an amplification reaction in which the probe serves as a template that

interacts with a separate primer for amplification. Thus, the Boyce-Jacino sequence reagent fails to include a primer-specific region, a capture region, and a target binding region.

Accordingly, the Examiner has failed to establish that the combination of Boyce-Jacino and Barany PCT would have motivated one of ordinary skill in the art to make the presently claimed probes or kits of independent claims 52, 60, 71, and 115.

Thus, the Examiner has failed to establish that Barany PCT and Boyce-Jacino would have shown or suggested claims 52, 60, 71, and 115, and all claims dependent from those claims. Thus, applicant need not address the Examiner's contentions concerning the other limitations of those claims. By not addressing those contentions, applicant in no way acquiesces to those contentions.

Applicant respectfully requests reconsideration and withdrawal of the § 103 rejections of certain claims in view of Barany PCT and Boyce-Jacino.

Rejection In View of Barany PCT and Boyce-Jacino and Xu

The Examiner also rejected several claims under 35 U.S.C. § 103(a) as allegedly being unpatentable over Barany PCT, in view of Boyce-Jacino, and further in view of Xu et al., *Tetrahedron Lett.*, 38(32):5595-5598 (1997) (Xu). See Action at page 10. The Examiner cited Barany PCT and Boyce-Jacino for the reasons discussed in the prior rejection and stated that Barany PCT and Boyce-Jacino did not teach use of tosylated or iodate oligonucleotides for ligation. See *id.* (Certain dependent claims specifically recite that "the 5' thymidine leaving group is tosylate or iodide.") The Examiner

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contended that Xu discussed tosylated and iodate oligonucleotides for ligation. See *id.* Applicant respectfully traverses.

All of the dependent claims that specifically recite that "the 5' thymidine leaving group is tosylate or iodide" ultimately depend from one of independent claims 52, 60, 71, or 115. Thus, all of those dependent claims include all of limitations of the claims from which they ultimately depend. Above, applicant explained why the Examiner failed to establish that Barany PCT and Boyce-Jacino would have suggested independent claims 52, 60, 71, and 115. Xu would have failed to remedy those deficiencies of Barany PCT and Boyce-Jacino.

Thus, the Examiner has failed to establish that the combination of Barany PCT, Boyce-Jacino, and Xu would have rendered obvious any of the rejected claims. Moreover, applicant need not address the Examiner's contentions concerning the combination of Barany PCT, Boyce-Jacino, and Xu with respect to other limitations of certain dependent claims. By not addressing those contentions, applicant in no way acquiesces to those contentions.

Applicant respectfully requests reconsideration and withdrawal of the § 103 rejections of certain claims in view of Barany PCT, Boyce-Jacino, and Xu.

Conclusion

Applicant respectfully asserts that the application is in condition for allowance and requests issuance of a Notice of Allowance. If the Examiner does not consider the application to be in condition for allowance, applicant requests that he call the undersigned at (650) 849-6620 to set up an interview.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: March 14, 2002

By: 

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